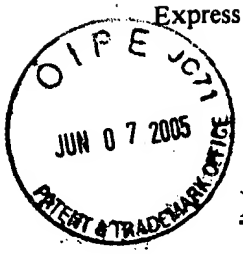
Express Mail Label No: EV 337 977 897 US

Docket Number: 39370.11



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kang Ting	Examiner:	Vanessa L. Ford
Serial No.:	09/912,297	Art Unit:	1645
Filed:	October 5, 1999		
Title:	NELL-1 ENHANCED BONE MINERALIZATION		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

Dear Examiner Ford:

In response to the Office Action mailed on November 17, 2004, please amend the claims and consider the remarks as follows. Accompanies this amendment is a petition to extend the time for response for three month to May 17, 2005, inclusive, and the appropriate fee associated therewith. Please address all future correspondence to

Zhaoyang Li, Ph.D., Esq.
Squire, Sanders & Dempsey LLP
One Maritime Plaza, Suite 300
San Francisco, California 94111

IN THE CLAIMS

1. (Currently amended) A method for an agent that modulates bone mineralization, said method comprising:

contacting an osteogenic cell expressing a NELL-1 gene with a test agent; and detecting an expression level of said NELL-1 gene in the contacted cell, where a difference in the expression level of NELL-1 in ~~a~~ an osteogenic cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization,

wherein the osteogenic cell is selected from the group consisting of an osteoblast, a mesenchymal cell, a fibroblast cell, a dura cell, a chondrocyte, a MC3T3 cell and a chondroblast.

2. (Previously amended) The method of claim 1, further comprising recording test agents that modulate expressions of the NELL-1 nucleic acid or NELL-1 protein in a database of test agents modulating NELL-1 activity or in a database of test agents modulating bone mineralization.

Claims 3-7 (withdrawn).

8. (Original) The method of claim 1, wherein said level of NELL-1 is detected by determining the expression level of a NELL-1 protein in said biological sample.

9. (Original) The method of claim 8, wherein said detecting is via a method selected from the group consisting of capillary electrophoresis, a Western blot, mass spectroscopy, ELISA, immunochromatography, and immunohistochemistry.

10. (Original) The method of claim 1, wherein said cell is cultured ex vivo.

11. (Original) The method of claim 1, wherein said test agent is not an antibody.

12. (Original) The method of claim 1, wherein said test agent is not a protein.

Claims 13-50 (withdrawn).

51. (Currently amended) The method of claim 1, wherein the osteogenic cell is ~~selected from~~ a cell endogenous to a fetal calvarial cell culture.

52. (Currently amended) A method for an agent that modulates bone mineralization, said method comprising:

contacting an osteogenic cell endogenous to a fetal calvarial cell culture expressing a NELL-1 gene with a test agent; and detecting an expression level of said NELL-1 gene in the contacted cell, where a difference in the expression level of NELL-1 in an osteogenic cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization,

~~The method of claim 51,~~ wherein the osteogenic cell is ~~selected from the group comprising an osteoblast, a mesenchymal cell, a fibroblast cell,~~ a stem cell~~,~~ or a bone marrow cell, ~~a dura cell, a chondrocyte, and a chondroblast~~.

53. Canceled.

54. (New) A method for an agent that modulates bone mineralization, said method comprising:

contacting an osteogenic cell expressing a NELL-1 gene with a test agent; and detecting an expression level of said NELL-1 gene in the contacted cell, where a difference in the expression level of NELL-1 in an osteogenic cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization.

REMARKS

Claims 1- 55 are pending in this application. Claims 2-7 and 13-50 were withdrawn. Claims 1, 2, 8-12 and 51-53 were rejected under 35 U.S.C. 112, first paragraph. Claim 51 was rejected as indefinite under 35 U.S.C. 112, second paragraph. Claim 54 is canceled.

Rejection under 35 U.S.C. 112, first paragraph

Claims 1, 2, 8-12 and 51-53 were rejected as lacking enablement under 35 U.S.C. 112, first paragraph. The Examiner alleged that the claimed method lack enablement where the osteogenic cell is a stem cell or a bone marrow cell.

The applicant submits that the claimed method is enabled under 35 U.S.C. 112, first paragraph. The Examiner maintained that bone marrow cell or a stem cell may not necessarily differentiate into osteogenic cells and thus the claimed method lacks enablement. The Examiner cited Bellows (Developmental Biology, 133:8-13, (1989)), Peterson et al. (U.S. Patent No. 6,200,606 B1), Caplan et al. (U.S. Patent No. 5,486,359), and Wobus (Molecular Aspects of Medicine, 22/3:149-164 (2001)), and Zhang et al. (The Journal of Clinical Investigation, 110(6):861-70 (2992)) to support the position that stem cells and bone marrow cells can, but may not necessarily, differentiate into fetal calvarial osteoblastic cells (see the Office Action mailed on November 17, 2004, p. 7, middle of the 3rd paragraph) and thus that the claimed method lacks enablement. The Examiner is in the position that Zhang, which states that anomalies were restricted to calvarial bone, despite generalized, non-tissue-specific over-expression of NELL-1, leads to the conclusion that the claimed method requires calvarial bone cells (see the Office Action mailed on November 17, 2004, p. 6, end of the first paragraph). The Examiner further alleged that the specification does not teach or disclose how bone marrow cells or stem cells can

be used in the claimed method when these cells may not actually differentiate into osteogenic cells (see the Office Action mailed on November 17, 2004, the paragraph bridging p. 6 and p. 7).

The applicant respectfully disagrees. Zhang only supports the readings that overexpression of NELL-1 in calvarial bone leads to calvarial anomalies and that overexpression of NELL-1 in tissues other than calvarial bone does not cause anomalies in these tissues. This is illustrated in the following from Zhang.: "Whole-mount skeletal staining did not show any observable extracranial skeletal anomalies. Hematoxylin and eosin and tartrate-resistant acid phosphatase staining of palatal and mid-mandible sutures, vertebrae, and long bones did not reveal any abnormal histology or increase in osteoclast number." (p. 865 first paragraph, second column) From the preceding section, it is apparent that the authors were primarily assaying for gross phenotypic differences in the animals and that the conclusions reached concern only "observable extracranial skeletal anomalies". Moreover, gross skeletal morphology is determined by not only by osteoblasts (form bone), but other cells types such as osteoclasts, which remove bone as well as complex epidermal-mesenchymal and possibly environmental interactions. Thus, although NELL-1 overexpression did not appear to cause grossly visible anomalies in tissues other than calvarial, in no way does this automatically support the Examiner's position that that no effect in mineralization was observed. Further, bone mineralization per se can occur in both normal and abnormal skeletal structures, and lacking anomalies skeletal structure has no direct bearing on the speed and degree of mineralization in an individual bone cell. Therefore, Zhang's observation that anomalies were restricted to calvarial bone, despite generalized, non-tissue-specific over-expression of NELL-1 does not support that the Examiner's position that bone mineralization caused by NELL-1 protein only occurs in calvarial bone cells.

Second, to practice the claimed method, there is no such requirement that a stem cell or a bone marrow cell must differentiate into an osteogenic cell only. As long as a stem cell or a bone marrow cell can differentiate into an osteogenic cell, the claimed method can be practiced. While the Examiner is correct that Bellows, Peterson, Caplan, and Wobus all evidence that stem cells or bone marrow cells can differentiate into cells other than osteogenic cells, these references equally evidence that stem cells or bone marrow cells, under a certain set of conditions, can differentiate into osteogenic cells. The conditions for a stem cell or a bone marrow cell to differentiate into a osteogenic cell have been well documented (see, as a few examples of the hundreds of reports in the field, Bianco, P., et al., "Multipotential cells in the bone marrow stroma: regulation in the context of organ physiology," Crit Rev Eukaryot Gene Expr. 9(2):159-73 (1999) (Review); Nordstrom, E., et al., "Osteogenic differentiation of cultured marrow stromal stem cells on surface of microporous hydroxyapatite based mica composite and macroporous synthetic hydroxyapatite," Biomed Mater Eng. 9(1):21-6 (1999); Sakai, A., et al., "Bone marrow cell development and trabecular bone dynamics after ovariectomy in ddy mice," Bone. 1998 Nov;23(5):443-51; Joyner, C.J., et al., "Identification and enrichment of human osteoprogenitor cells by using differentiation stage-specific monoclonal antibodies," Bone. 21(1):1-6 (1997); Krebsbach, P.H., et al., "Bone formation in vivo: comparison of osteogenesis by transplanted mouse and human marrow stromal fibroblasts," Transplantation 63(8):1059-69 (1997); Jaiswal, N., et al.," Osteogenic differentiation of purified, culture-expanded human mesenchymal stem cells in vitro," J Cell Biochem. 64(2):295-312 (1997)), which are part of the background knowledge that one of ordinary skill in the art would possess and that, according to the U.S. patent law, the applicant does not have to provide, and preferably should omit, in the specification (see, In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991);

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984); see also MPEP § 2164.01)). Accordingly, the specification provide enabling guidance for one of ordinary skill in the art to practice the claimed method. As such, the claimed method is enabled under 35 U.S.C. 112, first paragraph.

To facilitate the prosecution, claim 1 is amended to define that the osteogenic cell is one of an osteoblast, a mesenchymal cell, a fibroblast cell, a dura cell, a chondrocyte, a MC3T3 cell and a chondroblast. Claims 1, 2, 8-12 and 51-53, as amended, exclude a stem cell or a bone marrow cell from the definition of the osteogenic cell recited therein. As such, claims 1, 2, 8-12 and 51 are fully enabled and allowable.

Claim 52 is amended to define that the osteogenic cell is either a stem cell or a bone marrow cell. New claim 55 is added to define a method of screening for an agent that modulates bone mineralization using an osteogenic cell. As seen in the above discussion, the claimed method is enabled under 35 U.S.C. 112, first paragraph. As such, claims 52 and 55 are allowable.

Rejection under 35 U.S.C. 112, second paragraph

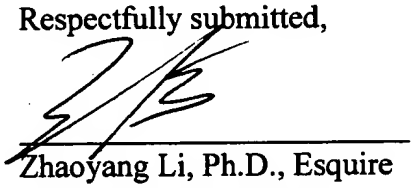
Claim 51 was rejected as indefinite in that the phrase "wherein the osteogenic cell is selected from a cell endogenous to a fetal calvarial cell culture" is allegedly unclear. Claim 51 is amended to delete the phrase and insert in place thereof "wherein the osteogenic cell is a cell endogenous to a fetal calvarial cell culture." The applicant submits that claim 51, as amended, is clear and definite.

Examination and allowance of the claims are respectfully requested. **If the Examiner has any suggestions or amendments to the claims to place the claims in condition for allowance, applicant would prefer a telephone call to Zhaoyang Li for approval of an Examiner's amendment.** If the Examiner has any questions or concerns, the Examiner is invited to telephone the undersigned attorney at (415) 393-9885.

Date: May 5, 2005

Squire, Sanders & Dempsey L.L.P.
One Maritime Plaza, Suite 300
San Francisco, CA 94111
Telephone (415) 393-9885
Facsimile (415) 393-9887

Respectfully submitted,



Zhaoyang Li, Ph.D., Esquire
Attorney for Applicants
Reg. No. 46,872